REMARKS

Claims 1-15, 51, 52, and 56-64 are pending in the application. Claims 65-71 are new. They recite limitations that are inherent to Enola, and the Court has held that "reference in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of §112, ¶ 1." *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed Cir. 2002). No new matter is introduced by these claims.

ELECTION/RESTRICTION

1. In light of the Request for Continued Examination, claims 16-50 and 53 drawn to a non-elected species remain withdrawn, and are not presently cancelled or appealed.

CLAIM REJECTIONS - 35 U.S.C. § 112, IST PARAGRAPH – WRITTEN DESCRIPTION

2. Claims 59 and 62, and claims 60, 61, 63 and 64 dependent thereon, stand rejected under 35 U.S.C. § 112, 1st paragraph, as failing to comply with the written description requirement. The Examiner specifically rejects language in claims 59 and 62 related to "yellow color plotted as a distribution in a population of the seed of sufficient number for purposes of ATCC deposit [having] a peak occurrence ranging" from one color to another color in the Munsell Book of Color. The Examiner states "these phrases were not present in the specification as originally filed, and the subject matter now claimed was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention."

There is no requirement that the phrases be recited *ipsis verbis* in the description. See, e.g. *Vas-Cath,* 8935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson,* 454 F.2d 746, 751,172 USPQ 391, 395 (CCPA 1972). One skilled in the relevant art would understand that a distribution of color in a population of seed is an inherent trait, and it has been determined that a deposit may be claimed according to the description of properties that are inherent to the deposit, even if those properties are not fully disclosed *in haec verba* in the original specification. *In re Nathan*, 328 F.2d 1005, 1008-1009, 140 USPQ 601, 604 (CCPA 1964) (the court holding that a later-added limitation

to the claims of the compound's alpha orientation was "an inherent characteristic" of the claimed subject matter to reverse a new matter rejection); *see Kennecott Corp. v. Kyocera Int'l, Inc.*, 835 F.2d 1419, 1421, (Fed. Cir. 1987) (holding that the disclosure in a subsequent patent application of an inherent property of a product does not deprive that product of the benefit of an earlier filing date because the addition is not new matter).

Distributions of phenotypes are discussed, for example, at the website http://www.mun/ca/biology/scarr/4241F_Quantitative_Genetics.html (July 18, 2005 printout is attached as Appendix A). There are "no clear cut borders for quantitative phenotypes, [we must] deal with a range of phenotypes. For this reason analysis involves measures of central tendency and dispersion." Phenotypic variance may be due to genetic and/or environmental variance such that a central tendency (mean, median or mode) may be identified and used to described the phenotype. The natural distribution of color in the seed coat of Enola with a peak (central tendency) in the recited range is shown in charts 15 and 31 of the Declaration of Gil Waibel (IDS of November 14, 2002, cite #1). It is appropriate that claims 59-64 describe inherent properties of the ATCC deposit.

Additionally, MPEP 2406.02 allows for deposit of biological material "after the effective filing date of an application for patent." A corroborating statement that the biological material that was deposited with the ATCC on December 11, 1997 is a biological material specifically identified in the application, as filed, was submitted in the response of January 27, 1998 in the file wrapper of U.S. Patent No. 5,894,079. There is antecedent basis in the patent specification, as of the filing date of the application, for the deposit of the biological material.

Patent Owner maintains that claims 59-64 fulfill the requirements of 35 U.S.C. § 112, 1st paragraph, written description. Reconsideration and withdraw of the rejection are respectfully requested.

3 - 4. The Examiner has rejected claims 1-15, 51, 52 and 56-64 under 35 U.S.C. § 112, 1st paragraph, as failing to comply with the written description requirement. We respectfully point out that, "A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the

examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97." (Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement, p. 17).

We do not believe that the Examiner has met the preponderance of evidence standard in stating that the "Patent Owner has not identified what feature or features distinguish the claimed seeds from other known *Phaseolus vulgaris* seeds" (Office Action, p. 6) and that "Patent Owner has not set forth what the uniform and stable characteristics are that distinguish the claimed seeds from other known *Phaseolus vulgaris* seeds." (Office Action, p. 7). The uniform and stable characteristics of the claimed seeds are clearly recited in the specification and claims. The uniform and stable characteristics include, for example:

- a seed coat that is yellow in color, where the yellow color is from about 7.5 Y 8.5/4 to about 7.5 Y 8.5/6 in the Munsell Book of Color when viewed in natural light.
- a hilar ring, where the hilar ring has a color of from about 2.5 Y 9/4 to about 2.5 Y 9/6 in the Munsell Book of Color when viewed in natural light.

The Examiner cites a typographical error in the patent specification that reads "The field bean cultivar Enola will *not* be described", instead of "*now* be described", and concludes that "Patent Owner has not described the claimed seeds and plants". This sentence is taken out of context and misconstrued. The next sentence in the paragraph reads, "The terminology used herein *to describe Enola* are those used by the Plant Variety Protection Office, ..." Clearly, Enola is described in the passages of Example 1 and Example 2 that directly follow, as well as by the remainder of the specification, the claims, the figures, and the ATCC deposit.

The Examiner states at page 8 of the instant Office Action "that Patent Owner has provided evidence that the deposited seeds have many traits that are not stable and uniform." In support of this view, the Examiner cites Patent Owner's statement that, "the seeds deposited with the ATCC are not the seeds of a single genetic entity. Rather the

seeds represent a variety of genetic entities, with a range of sizes, shapes and colors, both seed coat and hilar ring." It is well known that variation within a cultivar can produce a range of sizes, shapes and colors. See Appendix A. In accordance with the recognition that uniform and stable traits can best be described as a distribution, the specification of the '079 patent describes "*average* height of the mature plant" (col. 5, line 3), "*average* beak length of the pod" (col. 5, line 29), "number of seeds per pod is *approximately* 3.1", and color ranges from about 7.5 Y 8.5/4 to about 7.5 Y 8.5/6 and from about 2.5 Y 9/4 to about 2.5 Y 9/6 in the Munsell Book of Color when viewed in natural light for the seed coat and hilar ring, respectively. In ignoring normal variation among the individuals that make up a cultivar, the Examiner appears to be imposing a stringent test of stability and uniformity that borders on requiring clones. However, the Examiner has stated (Office Action, p. 7) that "the Office is not requiring exact [genetic] copies." Thus, the Office is not requiring exact genetic copies, yet neither will they accept normal variation within a cultivar. Patent Owner requests clarification.

Patent Owner has previously demonstrated "possession" of the invention based on the deposited material (*Enzo Biochem, Inc. v. Gen-Probe, Inc.,* 63 USPQ2d 1614 (Fed. Cir. 2002)), which may alone be sufficient to meet the written description requirement, and an exacting description of uniform and stable traits, which are clearly recited in the claims. Further, "possession may be shown by describing an actual reduction to practice of the claimed invention" (Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement, p. 9). An actual reduction to practice of the present invention was demonstrated by the ATCC deposit and documented in the drawings/photos of the patent application. (*Vas-Cath,* 935 F.2d at 1565, 19 USPQ2d at 1118 ("drawings alone may provide a 'written description' of an invention as required by Sec. 112")).

"An adequate written description of the invention may be shown by **any description of sufficient, relevant, identifying characteristics** so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." (Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement, p. 9) (emphasis added) citing *Purdue Pharma, L.P. v. Faulding Inc.,* 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1843 (Fed. Cir. 2000). The Examiner cites *University of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 916, 925, 69 USPQ2d 1886, 1893 (Fed. Cir. 2004) where the court held that the

University of California written description standard "applies to all types of inventions". We note that this ruling does not reverse, overrule or otherwise invalidate the decisions of the *Enzo* and *Moba* courts, and that the Office is not bound to any one ideology. Sufficient and relevant description of the Enola cultivar that identifies the stable and uniform characteristics of the plant appears in the '079 patent. The description is exacting enough that a potential infringer would know whether or not he was infringing, for example, by comparing the color of a potentially infringing field bean viewed in natural light to the Munsell Book of Color.

Patent Owner claims the field bean cultivar Enola according to recognizable phenotypes as described in the specification and shown by the inherent characteristics of the deposited material. The Patent Owner does not "intend to claim a large genus of genotypes and phenotypes that have not been described in the specification" as asserted by the Examiner (Office Action, p. 9).

The Patent Owner has previously stated and maintains that plant breeders select on the basis of phenotypes not genetic sequences. The Examiner states "that phenotypes are the functional expression of the genetic sequences comprised in a plant." (Office Action, p. 9). However, to "require a precise definition, such as by structure, formula, [or] chemical name" (*University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398 (Fed Cir. 1997)) of a genetic sequence that forms the basis for a plant phenotype would require a plant breeder or farmer to act in the capacity of a geneticist, molecular biologist, or biochemist. The standard of identifying a genetic sequence to determine a basis for a phenotypic trait is inequitable and places an undue burden on a plant breeder.

Patent Owner respectfully traverses the §112, first paragraph, written description rejection, for the reasons explained above, and requests withdrawal of the rejection.

Claim Rejections - 35 U.S.C. § 112, Ist Paragraph – Enablement

5 – 7. The Examiner has rejected claims 1-15, 51, 52 and 56-64 as invalid under 35 U.S.C. § 112, 1st paragraph, as failing to comply with the enablement requirement.

The Examiner refers to "a heterogeneous mix of seeds in the deposit" and "the deposit of a phenotypically varied population of seeds" (Office Action, pp. 11-12). As described above, the Enola cultivar comprises a plurality of individuals that share one or more uniform and stable traits. The heterogeneity of the seeds is on an individual basis

– they are not clones. The deposit contains a population of seeds displaying a normal variation in size, shape, color and other traits; the seeds are not phenotypically varied, but they display normal phenotypic variance. See Appendix A.

One of skill in the art could easily reproduce the claimed invention by accessing the ATCC deposit, as any seed on deposit would produce a plant of the claimed cultivar. All seeds on deposit belong to the Enola cultivar and a perfected deposit may be used for enablement purposes.

The Examiner states that the Declaration of Gil Waibel describes variation in Enola. Specifically, the Examiner notes that the primary color of seed coat addressed at item # 42 of the declaration asserts that "most" of the seed was in a color range described in the Plant Variety Protection application, which is different from the seed color range claimed and disclosed in the specification (Office Action, p.11). However, at point # 42 of the Declaration, Gil Waibel references charts 15 and 31, which clearly show that the peak occurrence of Enola seed coat color occurs between 7.5 Y 8.5/4 to 7.5 Y 8.5/6, as claimed and recited in the patent specification. In charts 15 and 31, 85% and 80% of the Enola seeds examined showed color in the 7.5 Y 8.5/4 to 7.5 Y 8.5/6 range.

Patent Owner respectfully traverses the §112, first paragraph, enablement rejection, for the reasons explained above, and requests withdrawal of the rejection.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

8 – 11. The Examiner has rejected claims 1-7, 57 and 59-64 under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Patent Owner regards as the invention.

The Examiner asserts that claim 1, and claims dependent thereon, are indefinite in view of Patent Owner's statement that the seeds deposited with the ATCC are not seeds of a single genetic entity. As discussed above, the seeds deposited with the ATCC are of a single cultivar (Enola), which is comprised of a plurality of individuals that have unique genetic profiles – the individuals are not clones. As "the Office is not requiring exact [genetic] copies" (Office Action, p. 7), Patent Owner fails to see the

validity of this rejection.

The Examiner also objects to "Patent Owner assert[ing] that they do not agree or disagree that the cultivar contains a uniform genotype." The Examiner then argues that by making this statement the "Patent Owner has admitted that the metes and bounds of the claimed invention are not clear." We respectfully disagree. According to the Merriam-Webster Online Dictionary, a genotype is all or part of the genetic constitution of an individual or group. Patent Owner has already stated that the Enola cultivar does not consist of individuals with identical (uniform) genetic constitutions (i.e., the Enola cultivar is not comprised of cloned plants). The Merriam-Webster Online Dictionary also defines a phenotype as the visible properties of an organism that are produced by the interaction of the genotype and the environment. Since the Enola phenotype is stable and uniform in multiple environments, we must assume that at least part of the genotype (responsible for the visible properties) is uniform.

12 - 14. Claim 10 is presently amended to provide proper antecedent basis. Claim 57 has been amended per Examiner's suggestion. Claims 59-64 have been listed as indefinite, but there is no explanation of the rejection. MPEP 707.07(d) states that "where a claim is refused for any reason relating to the merits thereof it should be 'rejected' **and the ground of rejection fully and clearly stated**..." (emphasis added). We accordingly ask for clarification in the manner dictated by the rules.

Patent Owner respectfully requests reconsideration of claims 1-7, 57 and 59-64 and withdraw of the 35 U.S.C. § 112, 2nd paragraph rejection.

Claim Rejections - 35 U.S.C. §§ 102/103

15 – 17. The Examiner has rejected claims 1-15, 51, 52 and 56-64 under 35 U.S.C. §102(b) as anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over CIAT G13 094, G02 400, G22 215, G22 227, G22 230, G11 891, or Kaplan (Guitarrero Cave, p. 146, 1980), or Hernandez-Xolocotzi et al. (Seminar Series 2E, CIAT, p. 253-258, 1973), or Voysest (Varieties of Beans in Latin America, CIAT, p. 47-50, 1983), or Gepts (The Genetic Resources of Phaseolus Beans, p. 602, 1988), or Azufrado Peruano 87 (Secretaria de Agricultura Y Recursos Hidraulicos; Solicitud de Inscripcion en el Registro Nacional de Variedades de Plantas, Registration No. FRI-150288-042,

September 25, 1987 at No. 52 and 53, in the IDS filed November 15, 2002).

The basis for the obviousness rejection is nowhere articulated. There is not even a suggestion as to what bean would be combined with what bean to make the claimed inventions obvious. The Examiner has not made out any case of obviousness -- much less the *prima facie* case required by law.

The Examiner's anticipation rejection suffers from essentially the same flaw, among others. As stated at ¶ 15, the Examiner bases the rejection on beans (or bean collections) that neither the Examiner nor the applicant has ever seen (Kaplan, Hernandez, Voysest or Gepts) (¶ 15). However, phantom references like these cannot support the Examiner's burden of making out a *prima facie* case of anticipation based on these references.

The Examiner's rhetoric cannot hide this basic failing. The Examiner supports her reliance on phantom references by a variety of arguments, including the argument that "the claimed bean seeds are clearly anticipated, as evidenced by the Polly Proctor Declaration, . . . and further given the subjective nature of color determination under conditions of natural light" (¶ 17 at p.20). The first point is nothing but bootstrapping, and the second is an attack on the very evidence that the Examiner relies upon to support the first argument -- the Polly Proctor Declaration.

Examiner also attempts to make her phantom references real by blaming applicant for failing to find them and test them (¶ 17 at p. 20). This is unsupportable. The burden is on the Examiner, not applicant. Nonetheless, the fact is that applicant has tried diligently to find prior art, and has been doing so since the earliest days of what turned out to be the Enola project. The Examiner has everything that applicant and his colleagues have been able to find, and they have so sworn honestly, repeatedly and under penalty of perjury. The Examiner apparently believes, without saying so directly, that they have sworn falsely.

A fifth phantom reference relied upon by Examiner is Peruano 87 (¶ 17 at p. 20). The Examiner's principal evidence on this subject is testimony of Dr. Pfeiffer (Pod-Ners' Response to Defendants' Motion to Compel) to the effect that the Enola bean *is* Peruano 87. There are several flaws in this approach. The testimony was given in litigation over applicant's Plant Variety Protection Certificate. By the time Dr. Pfeiffer gave the testimony, applicant had been involved in separate litigation with Dr. Pfeiffer over management of Pod-Ners, the company that owns the patent in issue here.

Finally, the cited testimony was taken by the defendants in the action, and applicant did not have an opportunity to cross-examine before the case settled. In short, Examiner has given full faith and credit to the deposition testimony of a highly biased witness who was never cross examined.

Beyond that, and ironically, Dr. Pfeiffer's testimony on the subject of Peruano 87 goes every which way. Here is some more of his testimony -- from the same deposition -- that directly contradicts the testimony cited by the Examiner:

> Q: What about the Peruano 87? Was that the closest out of – closest to the Enolas out of all of the varieties regardless of geographic location?
>
> A: I can't unequivocally say yes or no to that question because I don't know specifically the origin of the seed.

(Dr. Pfeiffer Depo., p. 287.)

Dr. Pfeiffer also explained that Pimono 78 was disclosed to the PVP Office rather than Peruano 87 because he did not have any Peruano 87 with which to compare to the Enola variety.

> Q: Why is it that you were able to tell the PVP Office that Pimono 78 was the closest?
>
> A: Because we had – originally the Bud originated from Mayocoba, as far as I know. And in the Mexican publication they had listed Pimono 78 as a Mayocoba, and that's the only other thing that we had that we could make any possible comparison to.

Dr. Pfeiffer also testified that he attempted to get some Peruano 87 seed in 1997 to make a color comparison with Enola. However, the seed that he obtained was treated and resulted in distorted and unreliable results. (Dr. Pfeiffer Depo., p. 300-01.)

Dr. Pfeiffer's uncertainty on the parentage was based in part on his experience that seed from Mexico, even allegedly registered seed, may not conform to its labeling.

> Q: So how do you know what it is?

A: Oftentimes you don't. Even if it says it's a variety, you are not even quite sure that's, quote, the variety because I don't think the Mexican government maintains their seed stock from – . . .

(Dr. Pfeiffer Depo., p. 148.)

Q: What was your concern about comparing it to the parents?

A: Essentially didn't know what the parentage was. The seed that was planted in Delta, Colorado, I still don't know what the parentage of that was specifically, and even if it, again, was a variety that originated in Mexico, my theory on seed out of Mexico is that what you see – what you get and what's actually in the bag may be two totally different things.

(Dr. Pfeiffer Depo., pp. 281-82.)

The Examiner next attempts to support her anticipation holding by relying on Polly Proctor's color analyses under the Munsell Book of Color (¶ 17). The analyses are based on nine specific, tangible beans that applicant was able to find and have tested by Ms. Proctor for the Examiner. As the Examiner admits, none of the readings fall within the scope of the claims. In the words of the patent, none of the nine beans "possesses a unique yellow color matching most closely to 7.5Y 8.5/4 to 7.5Y 8.5/6 in the Munsell Book of Color when viewed in natural light" (col.3, ll. 31-34; col. 1, l. 65 to col. 2, l. 4 (includes hilar ring)).

The Examiner notes that Ms. Proctor's evaluations for PI 282060, PI 312090 and PI 208777 do not specify whether the seed coat or the hilar ring was evaluated. The Examiner is referred to the Declaration of Polly Proctor filed March 25, 2003, where item 11 refers to the seed coat color of the GRIN beans, and to the P. Proctor Declaration submitted herewith. This information, however, does not aid the Examiner's anticipation case. Of the 111 readings taken, only one even fell on the 7.5Y page of the Munsell Book, and that single point was outside the claims.

The Examiner deals with this hole in her anticipation position by construing the term "about" in the numerical limitations of the claims. Although the Examiner does not say so explicitly, her claim construction plainly is meant to encompass Munsell color

squares that surround the two claimed squares -- 8.5/4 and 8.5/6 on page 7.5Y of the Munsell Book of Color. This construction is baseless. There is no support for it anywhere in the unusually large record in this matter. The Examiner's claim "construction" is made in a single sentence, and no supporting authority, factual or legal, is cited in support (¶ 17 at p. 18). It is an understatement to say that the Examiner has not carried her burden of making out a *prima facie* case of anticipation.

1. In his early work with the Enola bean, the applicant found that the seed coat color consistently fell on the 7.5Y page of the Munsell Book and consistently matched the 8.5/4 and 8.5/6 color sample squares on the 7.5Y page, which were next to one another (L. Proctor Dec. at 3). The match was not always perfect, however, because the two Munsell squares were two single colors and the beans were not always those exact colors. As the patent puts it: "Enola seed possesses a unique yellow color *matching most closely* to 7.5Y 8.5/4 to 7.5Y 8.5/6 in the Munsell Book of Color when viewed in natural light" (col.3, ll. 31-34; col. 1, l. 65 to col. 2, l. 4 (includes hilar ring))(emphasis added). The same general circumstances were observed with other parts of the Enola seed and plant (L. Proctor Dec. at 4).

2. The word "about" in the patent claims was put there to deal with this issue, which applicant specifically discussed with his patent lawyer (L. Proctor Dec. at 5). Applicant hoped that people would not be able to avoid his patent claims with beans that were not the exact shade of the squares he specified (L. Proctor Dec. at 5).

3. Applicant did not and does not intend, however, to try to stretch or distort "about" in such a way as to gain claim coverage of a bean matching some Munsell color square other than the specified 8.5/4 and 8.5/6 squares on the 7.5 Y page of the Munsell Book of Color (L. Proctor Dec. at 6). It was Mr. Proctor's understanding and intent that beans having, for example, a seed coat color of 7.5Y 8.5/8 or 7.5Y 8/6 would not fall within his claimed range of "about 7.5Y 8.5/4 to about 7.5Y 8.5/6" (L. Proctor Dec. at 6)

4. If applicant had been able to claim other nearby color squares, he would have done so (L. Proctor Dec. at 6). It is a rare patent applicant who wants anything but the broadest coverage for his inventions. But applicant's Enola beans fell into the two claimed color squares for the most part, and that was that. The color squares adjacent to the two claimed squares are markedly different colors (L. Proctor Dec. at 7 and Attachment 1 (7.5Y page of Munsell Book)).

Having attempted to make out a case of anticipation based on the work of Ms. Proctor, the Examiner then devotes considerable energy to discrediting Ms. Proctor's work on grounds of subjectivity, incompetence and bias (¶ 17 at 18) . It is difficult to know what to make of this. Accepting *arguendo* the Examiner's attack on Ms. Proctor, it follows that the Examiner's entire anticipation case is based on five phantom references that the Examiner has never seen and a color analysis that the Examiner considers to be worse than useless.[1] In short, the Examiner has made *no* case whatsoever of anticipation, colorable, *prima facie* or otherwise.

The Examiner provides an ISP address for a website that supposedly teaches that the Munsell color measurement system is to be used for comparison of color "with adjacent samples based upon equal perceived differences in color." Patent Owner respectfully believes that the Examiner has misunderstood the phrase "adjacent samples". The full quotation reads, "The MUNSELL system is a collection of color samples for comparison, with adjacent samples based upon equal perceived differences in color." Patent Owner believes that the "adjacent samples" referred to in the dependent clause of the sentence derive antecedent basis from the "color samples" referred to in the independent clause and that both terms refer to the 100 equally spaced hues around the circle (P. Proctor Dec. at 8). The claims are made relative to the Munsell Book of Color; it is therefore appropriate when determining whether existing seeds anticipate the claims that comparison is to the Munsell Book rather than to comparative Enola seeds. The seeds cited by the Examiner were properly examined against the Munsell Book of Color in natural light (P. Proctor Dec. at 2-8).

The Examiner expresses concern that "given the differing results of Bassett and Gepts with regard to identifying the parentage of Enola, ... the genetic makeup of Enola appears to be in question." Again, plant breeders select on the basis of phenotypes, not genetic sequences. The Enola cultivar displays uniform and stable traits that differ from other known cultivars.

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[1] Although probably not relevant for present purposes, Ms. Proctor is in fact a skilled colorist, with years of experience in reading bean colors. She has used the Munsell test because it was recommended by the Plant Variety Protection Office. When she visited the Munsell laboratories, she took the Farnsworth-Munsell Color test, a highly effective method for measuring any individual's color vision that has been used by the government and industry for over 40 years. The Examiner's discussion of color issues is incorrect in several respects (P.Proctor Dec. at 2-8).

The Examiner cites Pallotini et al. (Crop Science 44: 968-977, 2004) and states that "the results of their study indicate that the claimed Enola bean has an identical fingerprint to yellow-seeded beans from Mexico and is most similar to Azufrado Peruano 87" (Office Action p. 19). Respectfully, we also point out that the Pallotini article states, "Calculations of the probability of matching AFLP fingerprints showed that the most likely origin of Enola is by selection within pre-existing Mexican Peruano-type cultivars. This finding is consistent with the history of this genotype as outlined in the Enola patent and Appendix A of the PVP certificate...The uniformity of the AFLP banding pattern suggests that the sample submitted to the ATCC resulted from single seed selection during several generations before submission of the required seed sample to the ATCC." (p.976). The Pallotini article supports Patent Owner's position that Enola was produced through a selection process performed on beans, which were most likely of Mexican origin. We believe that Pallotini's conclusion resulted even though the study utilized selective and biased data, as explained below.

The Pallotini study is a regurgitation of the Expert Report of Paul Gepts, Ph.D., which was addressed by and submitted with the March 25, 2003 Declaration of Laura Conley. The Pallotini/Gepts study selectively analyzed Enola data from a "monomorphic" ATCC deposit, although the authors were clearly aware of at least two haplotypes within the ATCC material that they had in their possession (individuals #1 (Enola 2000-1), #52 (Enola 2000-2) and possibly #56 (Enola 2002) from Table 1 of the Pallotini article/Expert Report of Paul Gepts, Ph.D.; see specifically supporting data of Experiment 1 submitted as Exhibit B of the Laura Conley Declaration). Further, Figures 2 and 4 as shown in the Pallotini publication/Paul Gepts Report show polymorphism among Enola samples from all sources, e.g., Enola-1 (ATCC-USA), Enola-2001 (NFB-USA), Enola (NFB-USA). Patent Owner argues that by ignoring polymorphism within the Enola cultivar, Pallotini et al. created biased results that favored similarity between Azufrado Peruano 87 and Enola. Even after biasing the results, the authors found only a 30% chance that Enola resulted from selection without hybridization within the Azufrado Peruano 87 cultivar. These results are highly suspect and completely unconvincing.

Kaplan (Guitarrero Cave, p. 146, 1980) discloses a yellow *Phaseolus vulgaris* variety with median seed dimensions of 1.1 (length) x 0.79 (width) x 0.69 (thickness) cm, 4 seeds per pod and spherical pod morphology. Enola has an average seed length of 1.27 cm (based on a sample from Figure 1 of the '079 patent – scaled relative to a U.S. nickel), 3.1 seeds per pod and a pear shape cross section (col. 5, lines 26-31). Enola does not fit the characteristics of the variety disclosed by Kaplan.

Hernandez-Xolocotzi (Seminar Series 2E, CIAT, p. 253-258, 1973) discloses in Table 2 approximately 200 yellow *Phaseolus vulgaris* of various diameters as measured in millimeters. The values reported appear to be far too small for normal beans and no specific varieties are listed. We are unable to address a rejection based on such a vague publication. Further clarification or withdraw of the rejection is requested.

Voysest (Varieties of Beans in Latin America, CIAT, p. 47-50, 1983) discloses Canario, Azufrado and Azufrado Peruano varieties. Voysest lists all of the varieties as "medium size". According to his definition (p. 5) medium is "between 25 and 40 grams/100 seeds" and large is "from 40 grams/100 seeds". The '079 patent lists Enola as 43 grams per 100 seeds (col. 5, line 42) and the Declaration of Gil Waibel found the Enola seeds to be between 47-58 g/100 seeds, thus falling outside of the medium classification of the Canario, Azufrado and Azufrado Peruano varieties.

INFORMATION ASSESSMENT / REQUIREMENT FOR INFORMATION UNDER 37 C.F.R. § 1.105

The Examiner has mentioned a search done by Attorney Flores in the U.S. and Mexican Patent Offices with regard to two yellow bean varieties in 1993. We point out that this search was ordered by Dr. Pfeiffer on behalf of his company Agri Services, Inc. Both the Plaintiff and Defendant in the litigation agree that Patent Owner was not a client of Attorney Flores. "Pod-Ners, nor any of its representatives, had any communication with Mr. Flores." (Pod-Ners' Response to Defendants Motion to Compel, p. 49.) "Plaintiff [Pod-Ners] has produced no retainer agreement with Attorney Flores or any evidence at all to suggest that Attorney Flores even knows who Plaintiff or Larry Proctor are..." (Brief in Support of Defendant's Motion to Compel Plaintiff to Produce Documents of August 21, 2002, p. 27.) Patent Owner did not in 1993 and still does not have access to results of a search performed by Attorney Flores. There is no way it could have. It is privileged. Dr. Pfeiffer's counsel has asserted that privilege and it is

absolute until he says otherwise. (Pod-Ners' Response to Defendants Motion to Compel, p. 49.)

The Examiner has stated that papers provided by Patent Owner point to conflicting information with regard to how Patent Owner derived the claimed yellow beans. Applicant addressed this point in the last response:

> "Applicant planted the collection of yellow beans in 1991, and pursued a program of selective breeding for three generations. The invention was complete in 1993. For purposes of improving stability, applicant continued to selectively breed the invention through perhaps 1997. The patent states that the Mexican beans were acquired in 1994 and the breeding program started then. This is incorrect. It is an error. The same error was made in applicant's application for a Plant Variety Protection Act Certificate (of record in this proceeding)."

The Examiner also relies, once again, upon the testimony of Mr. Brunner, failing to recognize that Mr. Brunner's was the lead defendant in the PVP litigation with a strong motivation to dissemble. None of his talk was backed up with documentation, even when it was requested specifically by counsel (see generally L. Proctor Dec. of 6/2/2004 at 4).

The Examiner is continuing to require Patent Owner to provide any information available regarding the sale within the ambit of Patent Owner's control or that of a third party or the public use in the United States of the filed bean seeds originally obtained in Mexico. Regarding sales within the Patent Owner's ambit, Patent Owner developed his invention in secrecy and filed his application less than one year prior to his first public disclosure of his invention. Regarding sales by third parties and public use, Patent Owner is unaware of any such activities in the United States at the time of the original purchase and/or prior to the filing date of the instant patent. We traverse this continued request as "Any reply that states that the information required to be submitted is unknown and/or is not readily available to the party or parties from which it was requested will be accepted as a complete reply." (37 CFR § 1.105(a)(3)).

Conclusion

The Patent Owner has fully addressed the Examiners concerns relating to the specifications and claims. Authorization to charge fees associated with a request for continued examination, excess claim fees, and a three month extension of time is filed herewith. If additional fees are deemed necessary in connection with this response, the Examiner is authorized to charge deposit account number 12-0600. Please call the undersigned with any questions.

Respectfully submitted,

David J. Lee, Reg. No. 41,935
Lathrop & Gage, L.C.
4845 Pearl East Circle, Suite 300
Boulder, CO 80301
(720) 931-3021
(720) 931-3001 (fax)

CERTIFICATE OF SERVICE
37 C.F.R. §1.248

The undersigned certifies that on October 14, 2005, a copy of the foregoing amendment including all attachments was mailed by first class mail bearing sufficient postage to:

Dr. John H. Dodd's
Dodd's & Associates
1707 N. St. NW
Washington, D.C. 20036

The attachments include those specified in the amendment, additionally including a Petition for Three Months Extension of Time, Transmittal, Fee Transmittal, Certificate of Mailing.

David Lee
By: David J. Lee

10/14/05
Date

Quantitative Genetics

http://en.wikipedia.org/wiki/Quantitative_genetics

Sir Ronald Aylmer Fisher
http://www-gap.dcs.st-and.ac.uk/~history/Mathematicians/Fisher.html
http://instruct.uwo.ca/zoology/441a/hist3.html

Sewall Wright
http://instruct.uwo.ca/zoology/441a/hist4.html
http://www.amphilsoc.org/library/mole/w/wrights.htm

J.B.S. Haldane
http://instruct.uwo.ca/zoology/441a/hist5.html

Quantitative variation

Discontinuous traits: Traits that have only a few distinct phenotypes
Continuous traits: Traits that have continuous distributions of phenotypes

Quantitative vs Mendelian genetics:

Biometricians
- most variation in evolution didn't follow Mendelian rules
- continuous / blending variation that varies with environment
- Favors adaptation and survival of the fittest
- Mendelian traits are trivial and not interesting

Mendelians
- dismissed biometricians: genotype = phenotype?
- environmentally influenced = not inherited
- evidence supporting Mendelian genetics

Variation **is** continuous and can be inherited...
Continuous variation can be due to:
1. Numerous genes affecting expression (additive)
2. Environmental factors affecting expression (norm of reaction)
3. Both!

Multiple-factor hypothesis: many genes produce additive effect.
Polygenes: factors with small, equal effect
Polygenic traits: influenced by genetic variation at many loci
- analysis cannot be done by simple Mendelian genetics
- must compare phenotypic expression in close relatives (known to share a proportion of genes)

So what's environmental and what's genetic???

First a closer look **norm of reaction**...

Norm of Reaction

- relationship between environment and phenotype
- many phenotypes from one genotype under different environmental conditions
- phenotypes are constant in an environment (heritability measurements only apply to that environment)

To develop norm of reaction:
1. Develop a homozygous or stable heterozygous line (cloning, selfing)
2. Allow different lines to develop in different environments

Norm of reaction curves
- Plotting the phenotype of one genotype in each environment
- Determines the phenotypic distribution of the trait

Heritability of quantitative traits

Heritibility: the proportion of phenotypic variation due to genetic variation
Heritable - shared genotype
Familial - shared by a family (environmental)

But must account for environmental variation!!!!

Phenotypic variance (S_p^2) is due to genetic (S_g^2) and environmental (S_e^2) variance

$$\mathbf{S_p^2 = S_g^2 + S_e^2}$$

These variances can also be broken down to include:
- Additive genetic variance (alleles contributing to the genotype)
- Dominance variance (heterozygotes not always an intermediate phenotype)
- Interaction variance (epistatic interactions)
- Environmental variance: general effects, reversible effects and maternal effects
- Covariance between an environment and a genotype
- Genetic-environment interaction

Heritability, H^2 is the portion of the overall phenotypic variance due to genetics

$$\mathbf{H^2 = S_g^2 / S_p^2}$$
$$\mathbf{H^2 = S_g^2 / (S_g^2 + S_e^2)}$$

Non-zero heritability means genetic differences effect trait expression
Perfect heritability (ie: a high H^2) does not mean that the environment does not play a part in the variation

Limits of H^2...
- Limited prediction of the effect of environmental modification (better with norm of reaction)
- Separation of variance into genetic and environmental components doesn't separate the genetic and environmental causes of variation [http://www.mun.ca/biology/scarr/fig27-14.htm]
- high heritability does not mean that a trait is unaffected by its environment.

A trait may have perfect heritability and still change due to environmental variation
Example: IQ scores in adopted children, and their parents

Children	Biological parents	Adoptive parents
110	90	118
112	92	114
114	94	110
116	96	120
118	98	112
120	100	116
Mean = 115	**Mean = 95**	**Mean = 115**

Different Types of Variance That Affect Heritability

Heritability in the broad sense has limits on its usefulness.

We can examine heritability in the narrow sense.

Additive genetic variance: due to average differences between carriers of alleles of a QTL.

Dominance variance: due to fact heterozygotes are not always exact intermediates between homozygotes.

More than one locus acting on a character->*epistatic interactions*

These interactions will appear as *Interaction variance* (s^2_i).

interaction variance is included in dominance variance (nonadditive variance).

Genetic variance is the sum of additive and dominance variance:

$$s^2_g = s^2_a + s^2_d$$

So phenotypic variance:

$$s^2_p = s^2_a + s^2_d + s^2_e$$

More narrow sense of heritability: ratio of additive variance to the phenotypic variance:

$$h^2 = s^2_a / s^2_p$$

Whats the difference?!?

Heritability*(Broad Sense)* H^2: Phenotypic variance due to genetic variance.

Heritability*(narrow Sense)* h^2: Phenotypic variance due to **additive variance alone.**

Estimating Components of Genetic Variance

Hard to estimate all the components of genetic variance.

Easy way to estimate h^2.

Plot phenotype of offspring vs midparent value.

Midparent Value: Average phenotype of both parents.

- Regression line passes through mean of parent and offspring.
- Slope is positive.
- Slope is less than unity.
- Slope reprsesents heritability!!
- Heritability isn't perfect, so neither is slope!

Selection differential: Difference between parents and mean of entire population in the same generation.

Selection response: Difference between offspring and mean of entire population in the same generation.

Selection response = h^2 x Selection differential.

If we know other two can rearrange to solve for h^2!

Done with selective breeding.

h^2 will not be same for different populations in different environments.

Environment plays a role that can't be ignored!

h^2 and breeding

h^2 used widely in commercial breeding.

Good to make strong lines by selecting for or against traits.

Look for group with a lot of genetic variance for that trait.

Why?

- Group with a lot of genetic variance has high h^2
- Higher h^2 = higher parent-offspring correlation!
- Larger fraction of offspring will have wanted trait from parents!

Sometimes forced to work with low h^2.

When h^2 & H^2 both low:

- Lots of environmental variance!
- **Family selection** used!
- Pairs produce trial offsrping, rather than just best individuals.
- Parents selected from progeny that do best.
- Cancels out some of environmental variation.

When h^2 but H^2 high:

- Little environmental variance!
- More dominance variance than additive variance.
- Make use of nonadditive variance.
- **Hybrid-inbred method.**
- Lines made by self crossing.
- These lines are then crossed.
- Choose best hybrid from these crosses.
- Selects for both additive and dominance variance.

Experience with corn makes effectiveness questionable!

Locating Genes

Its not always possible to locate all the genes that influence a character!

- Only some subsets within a population will be variable.
- Only some variation is actually noticable (i.e Blood group genes).

- Interference from environment can cloud phenotypes.

Genetic analysis only detects a gene if there's variation at that loci.

Molecular analysis can examines DNA and the information it translates!

- We can than look at changes in stretches of DNA, whether phenotype varies or not
- Great for comparing different species!

candidate gene: known loci that *may* be responsible for *some* of the phenotypic variance.

Marker Gene Segregation

quantitative trait loci (QTL): Loci whose alleic differences cause variance in a character.

These quatitative trait loci cannot always be identified.

It is possible though to try and track down a region of a chromosome where these QTL's lie.

- cross two lines that differ markedly in QTL's as well as two well known "marker" loci
- If the marker gene is linked to the QTL we can use it to identify the QTL in the next generation.
- Marker genes can be used to "tag" regions of DNA where QTL's lie!

Linkage Analysis

Marker Gene segregation requires that marker genes are linked to the QTL.

Must be able to make parental lines differing in marker alleles.

Types of molecular polymorphisms used in linkage analysis:

- Restriction fragment length polymorphisms (RFLP's).
- Tandem repeats.
- Single-nucleotide polymorphisms (SNPs).

Such polymorphisms are very abundant.

Makes it likely that two lines will have some differences in known molecular marker loci.

Lines differing in quantitative traits have differences in polymorphisms as well!

How does Linkage analysis work exactly??

1. Make 2 lines differing in both marker loci and the quantitative trait in loci.

2. Cross the two lines.
3. Cross F1 to itself or backcrossed with parental line.
4. Measure offspring for quantitative phenotype.
5. Characterize genotype and marker loci.

Marker loci & QTL unlinked: All genotypes of the marker show the same average phenotype for the quantitative trait.

Marker loci & QTL are linked: Each marker genotype has different average phenotype.

Confused?

Think of it this way:

- Marker gene and QTL are unlinked: Independent assortment.
- Marker gene genotype has no bearing on the quantitative phenotype.
- Any marker genotype has the same spread of quantitative phenotypes with same average value.

But...

- If the two are linked then independent assortment doesnt occur!
- Certain alleles of the QTL will separate with certain genotypes of the marker.
- Average phenotype for the A allele is different than that of the a allele!
- Difference depends on strength of the QTL on the phenotype & tightness of the linkage.

If linked we now have a good idea what region the QTL lies in!!

Finding the gene(s) responsible is made much easier, but still a daunting task!!

The gene *may be one of many* influencing the trait, other genes may lie in different regions!

Works great in organisms like *Drosophila*, but human pedigrees are too small to work with!

LOD Scores

A **LOD score** is a type of statistic. that makes use of a probability ratio.

LOD scores are used to determine linkage distance.

The ratio is the probability of a birth sequence with a linkage of a certain distance divided by the probability of a birth sequence where the genes are unlinked.

The log of this ratio is then taken as a "LOD Score".

Linkage distances with the highest LOD scores are the best estimates of real linkage distances.

Working with logs a LOD score of 2.0 means that it is 100 times more likely.

An example of a LOD Score.

Multipoint Mapping

Multipoint mapping is an extension of linkage analysis.

Try to map loci in question against several markers at once!

Lets us know which side of marker loci is on!

LOD score consists of *combined* probabilities!

Makes it hard to compute, use computers!

Using only a few heterozygous loci can take monthes to analyze!!!

Othe tools used in quantitative genetics

Statistics

Statistical analysis is vital in quantitative genetics.

No clear cut borders for quantitative phenotypes, deal with a range of phenotypes.

For this reason analysis involves measures of central tendency and dispersion

Central Tendancy

Mean: Average value of a group.

Dispersion

Variance: How much something differs from the mean value.

Pedigrees

For comparing phenotypes between offspring we often use pedigrees.

A pedigree is basically a family.

Can be very useful in tracking quantitative phenotypes through multiple generations.

The small size of human pedigrees severly limits the accuracy of linkage analysis.

Today...

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http://content.karger.com/produktedb/produkte.asp?typ=fulltext&file=hhe49194

Questions?Email us!